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Enantioselective synthesis of natural products containing tertiary alcohols and contributions to a total synthesis of phorbacin B

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Chapter 2

Catalytic Asymmetric Synthesis of Dihydrofurans and Cyclopentenols with Quaternary Stereocenters

In this chapter, a novel asymmetric synthesis of dihydrofurans and cyclopentenols is described. Copper-catalyzed 1,2-addition of Grignard reagents to enones, combined with Sonogashira coupling/cyclization or ring-closing metathesis, provided two different kinds of dihydrofurans with medium to high enantioselectivities.

Parts of this chapter have been published:

Z. Wu, A. V. R. Madduri, S. R. Harutyunyan, A. J. Minnaard, *Eur. J. Org. Chem.* **2014**, 575-582.

2.1 Introduction

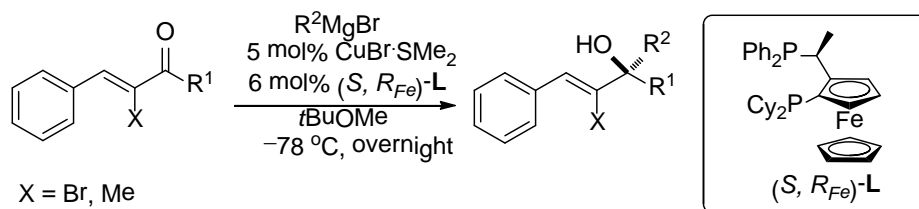
Functionalized chiral five-membered cyclic ethers, e.g. dihydro- and tetrahydrofuran derivatives, are ubiquitous structural units in natural products.^[1] Also due to their wide-spread applications,^[2] for example, as probe molecules for chemical reactions,^[3] in complex pharmaceuticals, and in commodity chemicals,^[2, 4] the synthesis of compounds containing chiral (dihydro)furans has been intensively studied.^[3, 5]

The asymmetric synthesis of five-membered ring ethers in which the oxygen is connected to a tertiary or quaternary stereocenter is of particular importance. Ring closing by face-selective attack of an oxygen nucleophile to an alkene is most commonly used. In this process, the alkene is activated either by Lewis acids including protonation,^[6] via allylic substitution,^[7] or conjugate addition^[8] or alternatively via ring-opening of the corresponding epoxide^[9] or haluronium ion.^[10] Alternatively, asymmetric ring-closing olefin metathesis has been applied.^[11]

For cyclic ether formation using the alternative approach, e.g. alkylation of a chiral tertiary alcohol followed by ring-closing, literature is particularly scarce. This is easily explained by the limited examples of effective methods for the enantioselective synthesis of the latter.

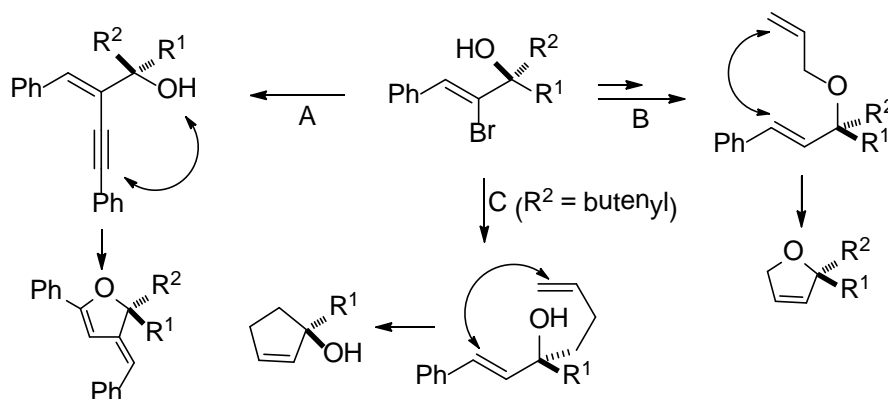
2.2 Strategies for chiral cyclic ether formation

Recently, our group reported on the use of a copper/Josiphos-type catalyst system to accomplish the enantioselective 1,2-addition of Grignard reagents to α,β -unsaturated ketones (Scheme 1).^[12] This leads to chiral enantioenriched tertiary allylic alcohols.^[13] We realized that upon subsequent alkylation on oxygen to the corresponding ethers, and together with suitable ring-closing reactions, this strategy will provide a useful method for the synthesis of chiral five-membered cyclic ethers. As the quaternary stereocenter formed is obviously not prone to racemization and not involved in the ring-closing reaction, the latter process should not lead to erosion of ee. As an additional task, we planned to unambiguously establish the absolute configuration of the tertiary alcohols and ethers formed in this way, as reliable data on these compounds are practically absent.



Scheme 1. Asymmetric Cu-catalyzed 1,2-addition of Grignard reagents to enones

Based on the product of the enantioselective 1,2-Grignard addition reaction, several approaches for ring-closure were selected (Scheme 2). In case the substituent X is bromide, it had already been shown that Sonogashira reaction readily leads to the corresponding enyne.^[12c] Base-induced intramolecular hydro-alkoxylation following a literature procedures^[14] leads then directly to substituted dihydrofurans (route A).



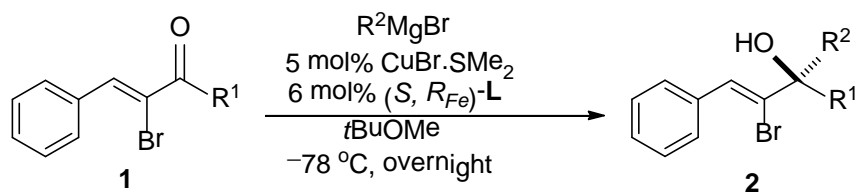
Scheme 2. Strategies for chiral cyclic ether formation

Upon allylation of the hydroxy group in the addition product, formally 1,6-dienes are formed. These should be very suitable substrates for ring-closing olefin metathesis, leading to chiral dihydrofurans with a double bond at the 3,4-position (route B). In turn, these out-of-conjugation alkenes can be further functionalized to provide highly substituted tetrahydrofurans.

Employing butenylmagnesium bromide in the asymmetric addition reaction gives a direct access to 1,6-dienes as well (route C). Although the enantioselectivity of the addition reaction in this particular case is less satisfactory (the reaction requires branched Grignard reagents to reach excellent ee values), we wanted to pursue this approach, as subsequent ringclosure via olefin metathesis leads to chiral allylic cyclopentenols. Formally, these originate from addition of a carbon nucleophile to cyclopentenone,^[15] but this reaction in an enantioselective fashion is not known. Alternatively, 1-methyl-2-cyclopentenol has been prepared from linalool using ring-closing metathesis.^[16]

2.3 Results and Discussion

The study commenced with the preparation of the enantioenriched tertiary allylic alcohols via catalytic asymmetric addition of Grignard reagents to the corresponding enones. These α -bromo enones **1**, in turn, are readily obtained by aldol condensation of benzaldehyde and the appropriate ketone, followed by dibromination/HBr elimination.^[17]



R ¹ (1)	R ²	2 *	yield (%)	ee (%)
Me (1a)	(CH ₃) ₂ CHCH ₂	2a	85	86
Ph (1b)	(CH ₃) ₂ CHCH ₂	2b	63	98
Me (1a)	Et ₂ CHCH ₂	2c	82	94
Me (1a)	CyCH ₂	2d	70	75

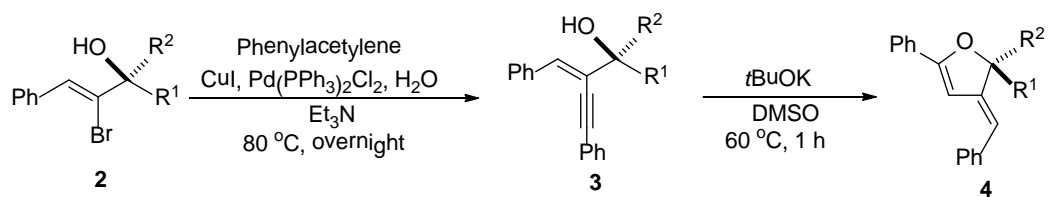
*The absolute configuration of **2** is *R*, vide infra.

Table 1. Asymmetric 1,2-addition to α -bromo enones **1**

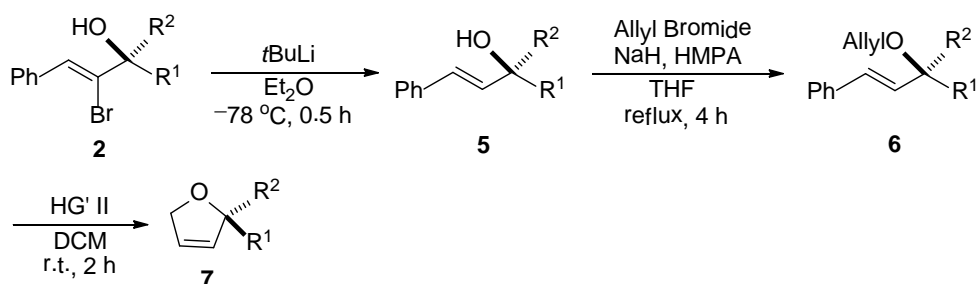
Upon treatment of the α -bromo enones **1a** and **1b** with isobutylmagnesium bromide in the presence of CuBr•SMe₂ (5 mol%) and (*S*, *R*_{Fe})-**L** (6 mol%) in methyl *tert*-butyl ether (MTBE) at -78°C , the desired chiral tertiary alcohols **2a** and **b** were obtained in good yields and good to excellent enantioselectivities (Table 1).^[12] In addition, **1a** was used in the addition of (2-ethyl)butylmagnesium bromide and cyclohexylmethylmagnesium bromide leading to the corresponding alcohols. As expected, the reactions could be performed on gram scale without deterioration in yield or ee except for **2d**, in which a longer reaction time led to a slightly lower ee.

With the products **2** in hand, the Sonogashira reactions, as part of route A, were carried out using 5 mol% Pd(PPh₃)₂Cl₂ and 10 mol% CuI as the catalysts in Et₃N. The corresponding enynes **3a-3d** were isolated in high yields (Table 2).^[18] Subsequent treatment with *t*BuOK in DMSO for 1 h at 60°C afforded the desired cyclized products **4a-d** in good yields.^[14a] It has been shown that 3-benzylidene-2,3-dihydrofurans are strongly fluorescent compounds.^[19]

Synthesis of the 2,5-dihydrofurans **7**, via route B, also started from the chiral tertiary alcohols **2**. Debromination with *t*BuLi in dry Et₂O at -78°C for 0.5 h,^[20] followed by aqueous work up, yielded the desired products **5a-c** in good isolated yields (Table 3). Alkylation of the hydroxyl groups in **5** turned out to be surprisingly difficult and substituents other than allyl could not be introduced. Under optimized conditions, comprising the use of 1.5 eq allyl bromide, 1.5 eq NaH and 3.0 eq HMPA in refluxing dry THF,^[21] **6a-c** were however prepared in high to excellent yield. Remarkably, **2d** refused to react under all conditions, presumable due to steric hindrance.



2	R ¹	R ²	3	yield (%)	4	yield (%)
2a	Me	(CH ₃) ₂ CHCH ₂	3a	88		80
2b	Ph	(CH ₃) ₂ CHCH ₂	3b	80		82
2c	Me	Et ₂ CHCH ₂	3c	92		91
2d	Me	CyCH ₂	3d	84		72

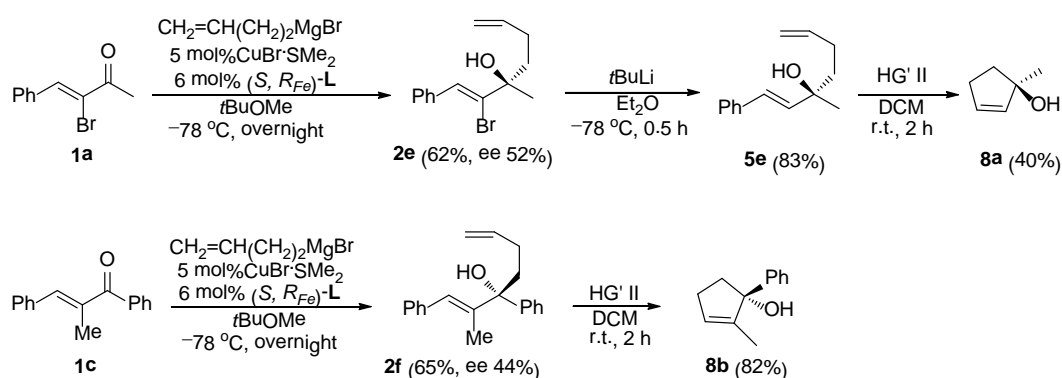
^a *E/Z* = 5 : 1**Table 2.** Synthesis of 3-benzylidene-2,3-dihydrofurans **4**

2	R ¹	R ²	5	yield (%)	6	yield (%)	7	yield (%)
2a	Me	(CH ₃) ₂ CHCH ₂	5a	84	6a	93		85
2b	Ph	(CH ₃) ₂ CHCH ₂	5b	87	6b	97		90
2c	Me	Et ₂ CHCH ₂	5c	82	6c	84		82

Table 3. Synthesis of 2,5-dihydrofurans **7**

Compounds **6a-c** were subsequently transformed into the corresponding 2,5-dihydrofurans **7a-c** by treatment with 5 mol% Hoveyda-Grubbs second generation catalyst in dichloromethane (Table 3).^[22] The reactions went fully selective to complete conversion and the high yields are probably only reduced because of the volatility of the products.

For the synthesis of cyclopentenols according to route C, butenylmagnesium bromide was added to **1a** and its α -methyl (instead of α -bromo) analogue **1c** (Scheme 3).^[12] Enantioselectivities were modest, as expected. Subsequent debromination of **2e**, following the procedure described earlier gave **5e** in 83% isolated yield. Subsequent ring-closing metathesis resulted in 1-methyl-2-cyclopentenol **8a**, in 40% yield, the moderate yield being solely due to its extreme volatility. Ring-closing of its congener **2f** gave **8b** in high yield.



Scheme 3. Synthesis of 2-cyclopenten-1-ols **8**

In order to determine the absolute configuration of this class of tertiary alcohols and ethers, we decided to prepare the corresponding α -hydroxy acids **9a-b** from **2a-b** and **2g** (Table 4). This would lead to known, well-described compounds and in itself, this approach might serve as an alternative route to chiral enantioenriched α,α -disubstituted acids which are important building blocks in natural product synthesis and normally prepared from chiral pool precursors. Hydroxy acid **9a** and **9b** were obtained from **2a** and **2b** in good yield by ozonolysis in acetone. The sign of their optical rotation, in comparison with the literature data, showed unambiguously that the (S,R_{Fe}) enantiomer of ligand **L** produces the *opposite* stereochemistry for $R^1 = \text{Me}$ than for $R^1 = \text{Ph}$, though both products are assigned the *R* configuration due to application of the CIP-rules. In the case of **2g**, ozonolysis was followed by a bromoform reaction which provided **9b** in low yield. For this substrate holds that the (S,R_{Fe}) enantiomer of **L** provides the same stereochemistry as for **2b** (in both cases R^1

is Ph), although the product (that is, the product of the 1,2 addition reaction, not the compound in Table 4) is designated *S* due to the CIP-rules.^[23]

R ¹ / X (2)	9	yield (%)	config. (2)
Me / Br (2a)	 9a	75	<i>R</i>
Ph / Br (2b)	 9b	86	<i>R</i>
Ph / Me (2g)	 9b	16	<i>S</i>

^a Reactions ii is only for the synthesis of **9b** from **2g**.

Table 4. Synthesis of α -hydroxy acids **9**

2.4 Conclusions

In summary, we have developed a novel approach for the enantioselective synthesis of chiral dihydrofurans with a tertiary oxygen-containing stereocenter and of tertiary cyclopentenols. Based on the catalytic asymmetric 1,2-addition of Grignard reagents, combined with a Sonogashira coupling/cyclization approach, or an alkylation followed by ring-closing metathesis, different kinds of dihydrofurans were prepared efficiently. With their absolute stereochemistry being established, the obtained compounds are versatile building blocks both for natural product synthesis and pharmaceuticals.

2.5 Experimental Section

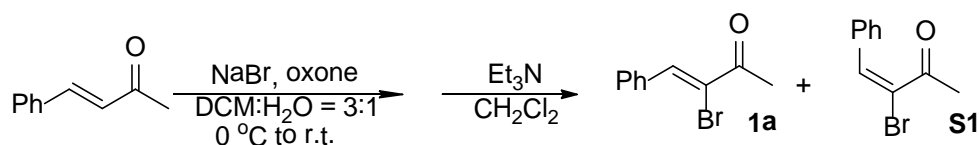
General remarks: ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) spectra were recorded with CDCl₃ as solvent. Chemical shifts were determined relative to the residual solvent peaks (CHCl₃, δ = 7.26 ppm for ¹H NMR, δ = 77.0 ppm for ¹³C NMR). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; qi, quintet; m, multiplet; br, broad. Enantiomeric excesses were determined by chiral HPLC in comparison with racemic products. Racemic products were obtained by the same procedure as used for the enantioselective 1,2-addition, but omitting the ligand and CuBr•SMe₂ (5 mol%) and

only using Grignard reagent (1.2 eq) at 0 °C in Et₂O. Regioselectivities were determined by ¹H NMR. Optical rotations were measured with a 10 cm cell (*c* given in g/100 mL) at 20 °C. Thin-layer chromatography (TLC) was performed on TLC Silica gel. Flash chromatography was performed on silica gel. Mass spectra were obtained from high resolution (ESI+ or APCI+) mass spectrometer. Copper salt was purchased and used without further purification. All starting materials, Copper salt, ligand (*S*, *R*_{Fe})-**L** and *i*BuMgBr (2 M in Et₂O) were purchased and used without further purification. All Grignard reagents were prepared from the corresponding alkyl bromides and Mg activated with I₂ in Et₂O.

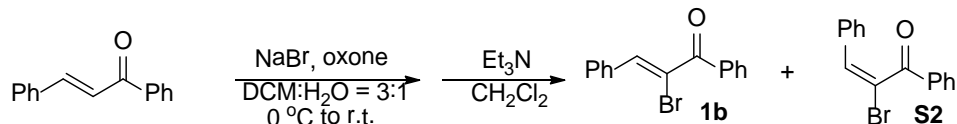
For the stereochemistry of α-bromo enones **1**, to our surprise, we could not find a rigorous proof of the stereochemistry of the so-obtained bromo enones in literature, despite the fact that these compounds have been reported several times. In this study the stereochemistry is determined unambiguously *a posteriori*. Upon catalytic asymmetric 1,2-addition using the bromo enones as substrate, the products are identical to the corresponding products obtained in the uncatalyzed addition with the same Grignard reagent, used to prepare the racemic reference material, so isomerisation during the Grignard addition can be excluded. After debromination of the resulting tertiary alcohols with *t*BuLi (*vide infra*), ¹H-NMR clearly shows the presence of an *E*-carbon-carbon double bond. This determines the stereochemistry of the starting bromo enones being as shown.

1a-c: Starting materials were prepared following literature procedures^[17].

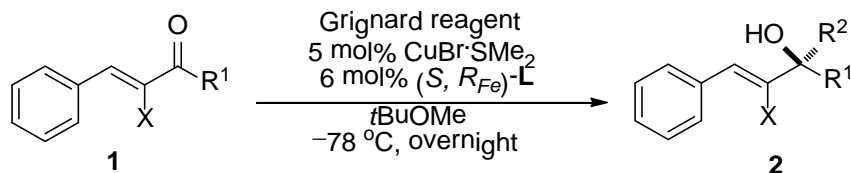
General procedure for the preparation of α-brominated enones: To a suspension of oxone (100 mmol) in dichloromethane (250 mL) and water (50 mL) was added portion-wise sodium bromide (100 mmol) over 10 min at 0 °C, and the resulting mixture was stirred for an additional 30 min. Then the enone (50 mmol) was added over 20 min and stirred overnight, allowing the reaction to warm to room temperature. The mixture was poured into water and extracted with dichloromethane. The combined organic phases were washed with water, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was dissolved in dry dichloromethane (100 mL) and the solution was treated with dry triethylamine (60 mmol) added dropwise via syringe over 10 min under nitrogen. After the addition was complete, the mixture was left stirring under nitrogen at room temperature for an additional 16 h. Then the mixture was washed with HCl (aq, 2 M) and brine, dried over Na₂SO₄, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane/EtOAc = 60 : 1) to afford the α-bromo-enone as a light yellow oil.



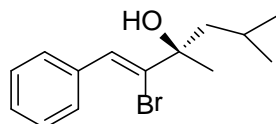
(Z)-3-Bromo-4-phenyl-3-buten-2-one (1a). 1a: yield 60%. ^1H NMR (400 MHz, CDCl_3) δ 8.03 (s, 1 H), 7.87–7.85 (m, 2 H), 7.44–7.43 (m, 3 H), 2.59 (s, 3 H); **(E)-3-Bromo-4-phenyl-3-buten-2-one (S1).** S1: yield 14%. ^1H NMR (400 MHz, CDCl_3) δ 7.35–7.34 (m, 3 H), 7.33 (s, 1 H), 7.27–7.34 (m, 2 H), 2.27 (s, 3 H).



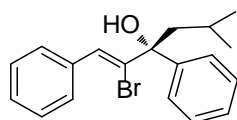
(Z)-2-Bromo-1,3-diphenyl-2-propen-1-one (1b). 1b: yield 78%. ^1H NMR (400 MHz, CDCl_3) δ 7.86–7.80 (m, 4 H), 7.70 (s, 1 H), 7.62–7.58 (m, 1 H), 7.49 (t, $J = 7.6$ Hz, 2 H), 7.45–7.42 (m, 3 H). **(E)-2-Bromo-1,3-diphenyl-2-propen-1-one (S2).** S2: yield 7%. ^1H NMR (400 MHz, CDCl_3) δ 8.01–7.97 (m, 2 H), 7.57–7.53 (m, 1 H), 7.45–7.40 (m, 2 H), 7.38 (s, 1 H), 7.19–7.16 (m, 5 H).



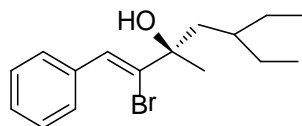
General procedure for the copper-catalysed 1,2-addition of Grignard reagents: A Schlenk tube equipped with septum and stirring bar was charged with $\text{CuBr}\cdot\text{SMe}_2$ (11.3 mg, 0.055 mmol, 5 mol%) and ligand (S, R_{Fe})-**L** (39.2 mg, 0.066 mmol, 6 mol%). Under nitrogen, dry $t\text{BuOMe}$ (8 mL) was added and the solution was stirred at room temperature for 15 min. Then the corresponding enone (1.10 mmol, in 5 mL $t\text{BuOMe}$) was added and the resulting solution was cooled to -78 °C. The corresponding Grignard reagent (1.32 mmol, 1.2 eq in Et_2O) was diluted with $t\text{BuOMe}$ (2 mL) and added to the reaction mixture over 3 h. The mixture was left to stir overnight at -78 °C. The reaction was quenched by the addition of MeOH and saturated aqueous NH_4Cl and the mixture was warmed to room temperature, diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O and the combined organic phases were dried over anhydrous Na_2SO_4 , filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane/ Et_2O = 20 : 1) to afford alcohol **2**.



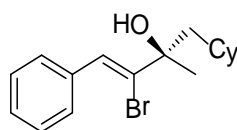
(R)-(Z)-2-Bromo-3,5-dimethyl-1-phenyl-1-hexen-3-ol (2a). Light yellow oil (265 mg, 85%). 86% ee determined by HPLC (Chiral AS-H column, heptane/*i*PrOH 90:10, 40 °C, 210 nm). Retention time: $t_{\text{major}} = 23.6$ and $t_{\text{minor}} = 22.5$ min. $[\alpha]_{\text{D}}^{20} = +10.0$ (c 1.04, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.56-7.54 (m, 2 H), 7.39-7.35 (m, 2 H), 7.32-7.28 (m, 1 H), 7.24 (s, 1 H), 2.01 (br s, 1 H), 1.89 (dd, $J = 14.0, 5.6$ Hz, 1 H), 1.84-1.78 (m, 1 H), 1.65 (dd, $J = 14.0, 6.0$ Hz, 1 H), 1.58 (s, 3 H), 1.00 (2 x d, $J = 6.4$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.2, 134.7, 129.0, 128.1, 127.7, 126.3, 77.6, 49.1, 28.8, 24.5, 24.2.



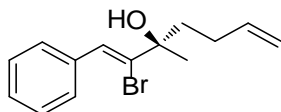
(R)-(Z)-2-Bromo-5-methyl-1,3-diphenyl-1-hexen-3-ol (2b). Light yellow oil (239 mg, 63%). 98% ee determined by HPLC (Chiral OD-H column, heptane/*i*PrOH 99:1, 40 °C, 230 nm). Retention time: $t_{\text{major}} = 21.9$ and $t_{\text{minor}} = 20.8$ min. $[\alpha]_{\text{D}}^{20} = -7.8$ (c 0.49, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 7.6$ Hz, 2 H), 7.56 (d, $J = 7.6$ Hz, 2 H), 7.43-7.32 (m, 7 H), 2.60 (s, 1 H), 2.23 (dd, $J = 14.4, 5.6$ Hz, 1 H), 2.14-2.09 (m, 1 H), 1.91-1.84 (m, 1 H), 1.08 (d, $J = 6.8$ Hz, 3 H), 0.89 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 144.4, 135.9, 134.9, 129.2, 128.3, 128.2, 128.0, 127.5, 126.0, 81.0, 48.0, 24.7, 24.5; HRMS (APCI) calcd. for $\text{C}_{19}\text{H}_{20}\text{Br}$ $[\text{M} - \text{OH}]^+$ 327.0743, found 327.0740.



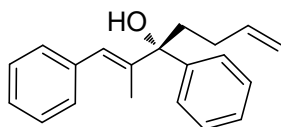
(R)-(Z)-2-Bromo-5-ethyl-3-methyl-1-phenyl-1-hepten-3-ol (2c). Light yellow oil (281 mg, 82%). 94% ee determined by HPLC (Chiral AS-H column, heptane/*i*PrOH 90:10, 40 °C, 210 nm). Retention time: $t_{\text{major}} = 16.0$ and $t_{\text{minor}} = 17.6$ min. $[\alpha]_{\text{D}}^{20} = +14.1$ (c 1.05, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.53 (d, $J = 7.2$ Hz, 2 H), 7.39-7.35 (m, 2 H), 7.32-7.28 (m, 1 H), 7.22 (s, 1 H), 1.98 (br s, 1 H), 1.87-1.83 (m, 1 H), 1.69-1.64 (m, 1 H), 1.59 (s, 3 H), 1.46-1.35 (m, 5 H), 0.90-0.86 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.3, 135.0, 129.0, 128.1, 127.6, 126.3, 77.6, 43.8, 36.4, 28.6, 26.5, 10.8; HRMS (ESI): calcd for $\text{C}_{16}\text{H}_{22}\text{Br}$ $[\text{M} - \text{OH}]^+$ 293.0905, found: 293.0879.



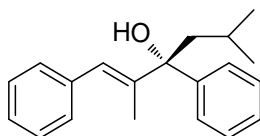
(R)-(Z)-3-Bromo-1-cyclohexyl-2-methyl-4-phenyl-3-buten-2-ol (2d). Light yellow oil (249 mg, 70%). 75% ee determined by HPLC (Chiral AD-H column, heptane/*i*PrOH 98:2, 40 °C, 250 nm). Retention time: $t_{\text{major}} = 25.1$ and $t_{\text{minor}} = 23.9$ min. $[\alpha]_{\text{D}}^{20} = +12.2$ (c 0.64, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.57 (d, $J = 7.2$ Hz, 2 H), 7.41-7.38 (m, 2 H), 7.34-7.30 (m, 1 H), 7.27 (s, 1 H), 2.18 (s, 1 H), 1.91-1.83 (m, 3 H), 1.74-1.65 (m, 4 H), 1.61 (s, 3 H), 1.56-1.49 (m, 1 H), 1.35-1.17 (m, 3 H), 1.13-1.03 (m, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.4, 134.9, 129.1, 128.1, 127.7, 126.3, 77.7, 48.0, 34.9, 34.7, 33.9, 28.8, 26.5, 26.3; HRMS (ESI) calcd. for $\text{C}_{17}\text{H}_{22}\text{Br}$ $[\text{M} - \text{OH}]^+$ 305.0899, found 305.0901.



(R)-(Z)-2-Bromo-3-methyl-1-phenyl-1,6-heptadien-3-ol (2e). Light yellow oil (191 mg, 62%). 52% ee determined by HPLC (Chiral AD-H column, heptane/*i*PrOH 98:2, 40 °C, 260 nm). Retention time: $t_{\text{major}} = 15.9$ and $t_{\text{minor}} = 14.1$ min. $[\alpha]_{\text{D}}^{20} = +4.8$ (c 0.58, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 7.9$ Hz, 2 H), 7.45-7.27 (m, 3 H), 7.21 (s, 1 H), 5.88 (m, 1 H), 5.19-4.83 (m, 2 H), 2.21-2.10 (m, 3 H), 2.10-1.98 (m, 1 H), 1.82 (m, 1 H), 1.57 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.4, 136.1, 133.7, 129.0, 128.1, 127.8, 126.8, 115.1, 77.3, 39.7, 28.4, 27.9; HRMS (ESI): calcd for $\text{C}_{14}\text{H}_{16}\text{Br}$ $[\text{M} - \text{OH}]^+$ 263.0436, found: 263.0431.

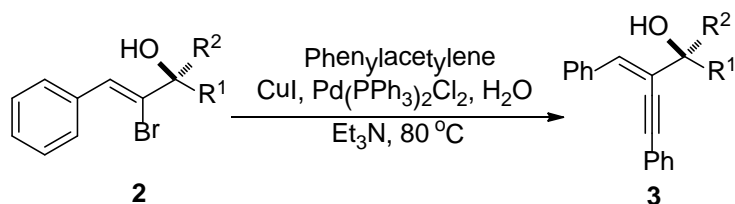


(S)-(E)-2-methyl-1,3-diphenyl-1,6-heptadien-3-ol (2f). Light yellow oil (199 mg, 65%). 44% ee determined by HPLC (Chiral AD-H column, heptane/*i*PrOH 98:2, 40 °C, 250 nm). Retention time: $t_{\text{major}} = 30.6$ and $t_{\text{minor}} = 27.8$ min. $[\alpha]_{\text{D}}^{20} = -19.4$ (c 0.95, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.50 (d, $J = 7.6$ Hz, 2 H), 7.38-7.22 (m, 8 H), 6.91 (s, 1 H), 5.97-5.87 (m, 1 H), 5.07 (d, $J = 17.2$ Hz, 1 H), 5.00 (d, $J = 10.4$ Hz, 1 H), 2.31-2.10 (m, 4 H), 1.97 (s, 1 H), 1.67 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.1, 141.7, 138.9, 138.1, 129.1, 128.2, 128.1, 127.1, 126.4, 125.9, 124.8, 114.8, 79.6, 38.0, 28.2, 15.1; HRMS (APCI) calcd. for $\text{C}_{20}\text{H}_{21}$ $[\text{M} - \text{OH}]^+$ 261.1638, found 261.1639.

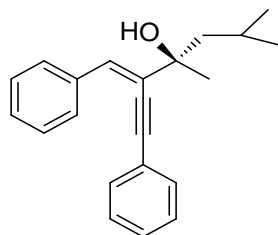


(S)-(E)-2,5-Dimethyl-1,3-diphenyl-1-hexen-3-ol (2g). Light yellow oil (188 mg, 61%). 37% ee determined by HPLC (Chiral OD-H column, heptane/*i*PrOH 98:2,

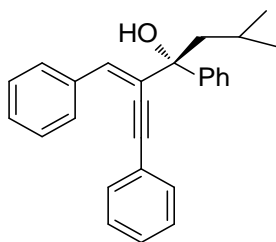
40 °C, 250 nm). Retention time: $t_{\text{major}} = 14.1$ and $t_{\text{minor}} = 14.5$ min. $[\alpha]_{\text{D}}^{20} = -16.3$ (c 0.32, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.38 (m, 2 H), 7.25-7.08 (m, 8 H), 6.81 (s, 1 H), 2.03 (dd, $J = 14.4, 5.6$ Hz, 1 H), 1.93 (dd, $J = 14.4, 5.6$ Hz, 1 H), 1.75-1.70 (m, 2 H), 1.55 (d, $J = 0.8$ Hz, 3 H), 0.91 (d, $J = 6.8$ Hz, 3 H), 0.80 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.9, 142.4, 138.3, 129.1, 128.16, 128.11, 126.9, 126.3, 125.9, 124.4, 80.1, 47.2, 24.84, 24.83, 24.2, 15.4; HRMS (ESI) calcd. for $\text{C}_{20}\text{H}_{23} [\text{M} - \text{OH}]^+$ 263.1794, found 263.1800.



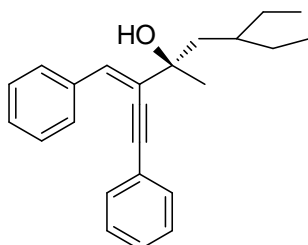
General procedure for the Pd-catalyzed synthesis of enynes^[18]: To a solution of **2** (0.50 mmol) in Et_3N (5 mL) was added $\text{Pd(PPh}_3)_2\text{Cl}_2$ (17.5 mg, 0.025 mmol, 5 mol%), CuI (9.5 mg, 0.050 mmol, 10 mol%), phenylacetylene (0.082 mL, 0.75 mmol, 1.5 eq) and H_2O (0.045 mL, 2.5 mmol, 5 eq), and the resulting mixture was stirred at 80 °C. The solvent was evaporated under reduced pressure after the starting material had been consumed and the residue was diluted with Et_2O and washed with saturated aqueous NH_4Cl . The organic layer was separated, and the aqueous layer was extracted with Et_2O . The combined organic layers were dried over Na_2SO_4 , concentrated in vacuo, and the residue was purified by column chromatography on silica gel (pentane/ $\text{Et}_2\text{O} = 12 : 1$) to afford enyne **3**.



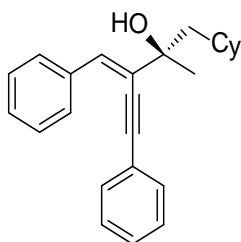
(R)-3-[(E)-benzylidene]-4,6-dimethyl-1-phenyl-1-heptyn-4-ol (3a). Light brown oil (134 mg, 88%). $[\alpha]_{\text{D}}^{20} = +24.2$ (c 0.48, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.94 (d, $J = 8.0$ Hz, 2 H), 7.51-7.49 (m, 2 H), 7.42-7.37 (m, 5 H), 7.32-7.29 (m, 1 H), 7.10 (s, 1 H), 1.99 (dd, $J = 14.0, 5.6$ Hz, 1 H), 1.92-1.86 (m, 1 H), 1.81 (br s, 1 H), 1.74-1.69 (m, 1 H), 1.60 (s, 3 H), 1.04-1.00 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.5, 131.8, 131.3, 128.9, 128.5, 128.4, 128.2, 128.0, 126.3, 123.4, 97.5, 88.1, 76.5, 50.1, 29.6, 24.6, 24.52, 24.50; HRMS (ESI) calcd. for $\text{C}_{22}\text{H}_{23} [\text{M} - \text{OH}]^+$ 287.1794, found 287.1795.



(R)-3-[(E)-Benzylidene]-6-methyl-1,4-diphenyl-1-heptyn-4-ol (3b). Light brown oil (147 mg, 80%). $[\alpha]_D^{20} = +28.0$ (*c* 1.18, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.82-7.80 (m, 2 H), 7.55-7.52 (m, 2 H), 7.28-7.12 (m, 11 H), 7.05 (s, 1 H), 2.31 (dd, $J = 14.4, 5.6$ Hz, 1 H), 2.20 (br s, 1 H), 2.04 (dd, $J = 14.4, 5.6$ Hz, 1 H), 1.86-1.79 (m, 1 H), 0.96 (d, $J = 6.8$ Hz, 3 H), 0.86 (d, $J = 6.8$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 145.9, 136.4, 132.9, 131.3, 129.0, 128.50, 128.46, 128.43, 128.22, 128.21, 128.1, 127.1, 125.9, 123.3, 98.1, 88.2, 79.5, 48.5, 24.9, 24.8, 24.5; HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{25}$ $[\text{M} - \text{OH}]^+$ 349.1951, found 349.1948.

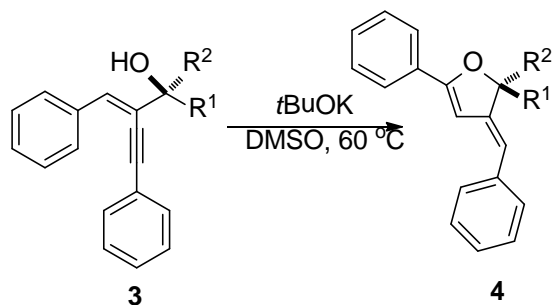


(R)-3-[(E)-benzylidene]-6-ethyl-4-methyl-1-phenyl-1-octyn-4-ol (3c).^[12c] Light brown oil (152 mg, 92%). $[\alpha]_D^{20} = +51.6$ (*c* 1.80, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 8.02-7.84 (m, 2 H), 7.59-7.26 (m, 8 H), 7.07 (s, 1 H), 2.06-1.88 (m, 2 H), 1.78 (s, 1 H), 1.60 (s, 3 H), 1.54-1.28 (m, 5 H), 0.88 (t, $J = 7.2$ Hz, 3 H), 0.72 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.6, 131.8, 131.3, 129.2, 128.9, 128.44, 128.37, 128.2, 128.1, 127.9, 123.4, 97.4, 88.2, 76.5, 44.7, 36.3, 29.3, 26.9, 10.8; HRMS (ESI): calcd for $\text{C}_{24}\text{H}_{27}$ $[\text{M} - \text{OH}]^+$ 315.2113, found: 315.2107.

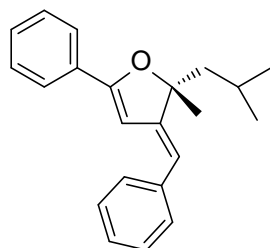


(R)-3-[(E)-benzylidene]-1-cyclohexyl-2-methyl-5-phenyl-4-pentyn-2-ol (3d). Light brown oil (145 mg, 84%). $[\alpha]_D^{20} = +37.6$ (*c* 1.20, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.84-7.82 (m, 2 H), 7.40-7.38 (m, 2 H), 7.32-7.25 (m, 5 H), 7.23-7.22 (m, 1 H), 6.98 (s, 1 H), 1.88-1.83 (m, 1 H), 1.75 (d, $J = 12.4$ Hz, 2 H), 1.67 (s, 1 H), 1.62-1.56 (m, 3 H), 1.53 (d, $J = 1.2$ Hz, 1 H), 1.49 (s, 3 H), 1.18-1.08 (m, 3 H), 1.07-0.92 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 136.6, 131.7, 131.3, 129.2, 128.8,

128.43, 128.37, 128.2, 127.9, 123.4, 97.4, 88.1, 76.5, 48.9, 35.2, 34.8, 33.8, 29.5, 26.4, 26.3; HRMS (ESI) calcd. for $C_{25}H_{27}$ $[M - OH]^+$ 327.2107, found 327.2107.

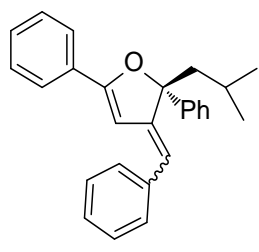


General procedure for cyclization of the enyne^[14a, 19]: To a solution of **3** (0.25 mmol) in DMSO (4.0 mL) was added *t*BuOK (31 mg, 0.275 mmol, 1.1 eq) and the resulting mixture was stirred at 60 °C for 1 h. The mixture was poured into water (50 mL) and extracted with Et₂O. The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane) to afford **4**.



(R)-3-[(E)-Benzylidene]-2-isobutyl-2-methyl-5-phenyl-2,3-dihydrofuran (4a).

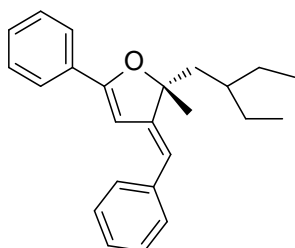
Yellow oil (61 mg, 80%). $[\alpha]_D^{20} = +27.6$ (*c* 2.05, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.63 (dd, *J* = 8.4, 1.6 Hz, 2 H), 7.32-7.24 (m, 7 H), 7.10-7.05 (m, 1 H), 6.55 (s, 1 H), 5.62 (s, 1 H), 1.81-1.71 (m, 2 H), 1.62-1.57 (m, 1 H), 1.41 (s, 3 H), 0.86 (dd, *J* = 11.2, 6.4 Hz, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 163.0, 150.5, 139.1, 130.8, 129.3, 128.49, 128.45, 127.5, 125.7, 125.5, 111.6, 98.7, 91.9, 50.1, 28.2, 24.6, 24.5, 24.3; HRMS (APCI) calcd. for $C_{22}H_{25}O$ $[M + H]^+$ 305.1900, found 305.1905.



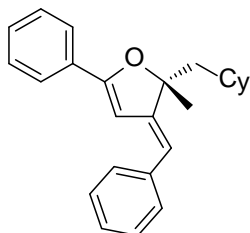
4b. Yellow oil (75 mg, 82%, *Z/E* = 5/1). $[\alpha]_D^{20} = +41.1$ (*c* 0.94, CHCl₃); HRMS (ESI) calcd. for $C_{27}H_{27}O$ $[M + H]^+$ 367.2056, found 367.2055;

(R)-3-[(E)-Benzylidene]-2-isobutyl-1,5-diphenyl-2,3-dihydrofuran [4b(E)]. ¹H NMR (400 MHz, CDCl₃) δ 7.86 (dd, *J* = 7.2, 1.2 Hz, 2 H), 7.59-7.57 (m, 2 H),

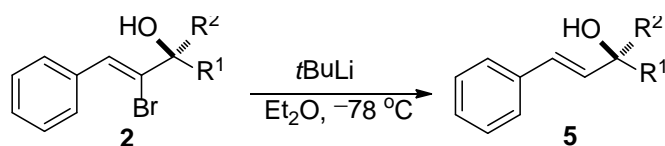
7.49-7.37 (m, 10 H), 7.22-7.18 (m, 1 H), 6.73 (s, 1 H), 6.00 (s, 1 H), 2.39-2.34 (m, 1 H), 2.18-2.12 (m, 1 H), 2.02-1.96 (m, 1 H), 1.08-1.06 (m, 3 H), 1.02 (dd, $J = 6.8, 1.6$ Hz, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.2, 149.5, 144.3, 138.7, 130.4, 129.5, 128.6, 128.5, 128.4, 127.8, 127.3, 125.8, 125.5, 124.8, 114.3, 98.9, 94.1, 49.4, 29.8, 24.9, 24.6. **(R)-3-[(Z)-Benzylidene]-2-isobutyl-1,5-diphenyl-2,3-dihydrofuran [4b(Z)]**. ^1H NMR (400 MHz, CDCl_3) δ 7.70-7.68 (m, 0.40H), 7.63-7.61 (m, 0.40 H), 7.49-7.37 (m, 0.20 H), 7.33-7.29 (m, 1.00 H), 7.12-7.11 (m, 0.60 H), 6.95-6.93 (m, 0.40 H), 6.61 (s, 0.20 H), 6.27 (s, 0.20 H), 2.39-2.34 (m, 0.40 H), 2.02-1.96 (m, 0.20 H), 1.08-1.02 (m, 1.20 H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.0, 148.9, 143.6, 137.1, 130.5, 129.1, 128.5, 128.0, 127.8, 126.4, 125.9, 125.6, 117.2, 105.9, 93.5, 42.9, 29.4, 25.0, 24.9.



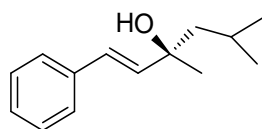
(R)-3-[(E)-Benzylidene]-2-(2-ethyl-butyl)-2-methyl-5-phenyl-2,3-dihydrofuran (4c).^[12c] Yellow oil (76 mg, 91%). $[\alpha]_{\text{D}}^{20} = +37.7$ (c 0.90, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.82-7.65 (m, 2 H), 7.37 (m, 7 H), 7.17 (t, $J = 7.1$ Hz, 1 H), 6.64 (s, 1 H), 5.73 (s, 1 H), 1.76 (m, 2 H), 1.50 (s, 3 H), 1.42-1.24 (m, 5 H), 0.80 (t, $J = 7.1$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.0, 150.5, 139.1, 130.7, 129.3, 128.5, 128.4, 127.5, 125.7, 125.4, 111.6, 98.7, 92.0, 44.5, 36.4, 28.1, 26.8, 26.5, 10.9.



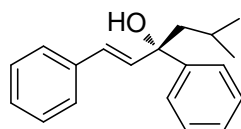
(R)-3-[(E)-Benzylidene]-2-cyclohexyl-2-methyl-5-phenyl-2,3-dihydrofuran (4d). Yellow oil (62 mg, 72%). $[\alpha]_{\text{D}}^{20} = +41.4$ (c 1.07, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.62 (d, $J = 6.8$ Hz, 2 H), 7.32-7.24 (m, 7 H), 7.08 (t, $J = 7.2$ Hz, 1 H), 6.54 (s, 1 H), 5.62 (s, 1 H), 1.77-1.71 (m, 1 H), 1.68 (d, $J = 5.6$ Hz, 1 H), 1.65-1.60 (m, 1 H), 1.58-1.49 (m, 4 H), 1.40 (s, 3 H), 1.18-0.88 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.0, 150.7, 139.1, 130.8, 129.3, 128.50, 128.45, 127.5, 125.7, 125.5, 111.6, 98.6, 91.9, 48.8, 34.8, 34.7, 33.9, 28.1, 26.44, 26.39; HRMS (ESI) calcd. for $\text{C}_{25}\text{H}_{29}\text{O}$ $[\text{M} + \text{H}]^+$ 345.2213, found 345.2211.



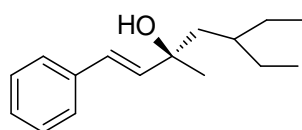
General procedure for the preparation of α,β -unsaturated alcohols^[20]: To a solution of **2** (0.55 mmol) in Et₂O (5.0 mL) was slowly added a solution of *t*BuLi (1.65 mmol, 3.0 eq, 1.7 M in pentane) under nitrogen at $-78\text{ }^{\circ}\text{C}$, and the resulting mixture was stirred at this temperature for 30 min. Then the reaction was quenched with MeOH and saturated aqueous NH₄Cl, and the mixture was warmed to room temperature, diluted with Et₂O and the layers were separated. The aqueous layer was extracted with Et₂O and the combined organic phase was dried over Na₂SO₄, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane/Et₂O = 20 : 1) to afford alcohol **5**.



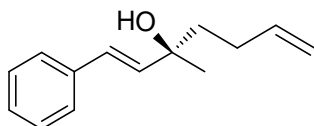
(*R*)-(*E*)-3,5-Dimethyl-1-phenyl-1-hexen-3-ol (5a). Light yellow oil (94 mg, 84%). $[\alpha]_{\text{D}}^{20} = +32.4$ (*c* 0.53, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, *J* = 7.6 Hz, 2 H), 7.35-7.31 (m, 2 H), 7.24 (t, *J* = 7.2 Hz, 1 H), 6.61 (d, *J* = 16.0 Hz, 1 H), 6.31 (d, *J* = 16.0 Hz, 1 H), 1.84-1.79 (m, 1 H), 1.62 (br s, 1 H), 1.59 (d, *J* = 6.0 Hz, 2 H), 1.40 (s, 3 H), 1.00-0.96 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.3, 137.2, 128.6, 127.3, 126.5, 126.4, 73.7, 51.6, 29.2, 24.63, 24.59, 24.45; HRMS (ESI) calcd. for C₁₄H₁₉ [M – OH]⁺ 187.1481, found 187.1480.



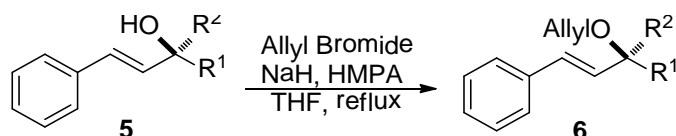
(*S*)-(*E*)-5-methyl-1,3-diphenyl-1-hexen-3-ol (5b). Light yellow oil (127 mg, 87%). $[\alpha]_{\text{D}}^{20} = +18.8$ (*c* 0.49, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.56 (d, *J* = 7.6 Hz, 2 H), 7.44-7.25 (m, 8 H), 6.70 (d, *J* = 16.0 Hz, 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 2.06-2.01 (m, 1 H), 2.01 (br s, 1 H), 1.95 (dd, *J* = 14.4, 6.0 Hz, 1 H), 1.84-1.78 (m, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.3, 137.0, 136.6, 128.6, 128.3, 127.5, 127.4, 126.8, 126.6, 125.5, 77.5, 51.3, 24.6, 24.3; HRMS (APCI) calcd. for C₁₉H₂₁ [M – OH]⁺ 249.1638, found 249.1634.



(R)-(E)-5-Ethyl-3-methyl-1-phenyl-1-hepten-3-ol (5c). Light yellow oil (105 mg, 82%). $[\alpha]_D^{20} = +38.7$ (*c* 0.45, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.39 (d, *J* = 7.2 Hz, 2 H), 7.35-7.31 (m, 2 H), 7.25-7.22 (m, 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.30 (d, *J* = 16.0 Hz, 1 H), 1.61-1.58 (m, 3 H), 1.42 (s, 3 H), 1.42-1.34 (m, 5 H), 0.89-0.83 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.3, 137.2, 128.6, 127.3, 126.5, 126.4, 73.8, 46.3, 36.3, 29.0, 27.0, 26.9, 10.8; HRMS (ESI) calcd. for C₁₆H₂₃ [M – OH]⁺ 215.1794, found 215.1793.

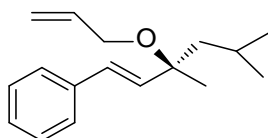


(R)-(E)-3-methyl-1-phenyl-1,6-heptadien-3-ol (5e). Light yellow oil (92 mg, 83%). $[\alpha]_D^{20} = +9.1$ (*c* 1.95, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.22 (m, 5 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.28 (d, *J* = 16.0 Hz, 1 H), 5.91-5.81 (m, 1 H), 5.05 (d, *J* = 17.6 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 2.20-2.14 (m, 2 H), 1.76-1.72 (m, 3 H), 1.41 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 138.8, 136.9, 136.4, 128.6, 127.4, 127.3, 126.4, 114.6, 73.3, 41.7, 28.6, 28.4; HRMS (ESI) calcd. for C₁₄H₁₇ [M – OH]⁺ 185.1325, found 185.1322.



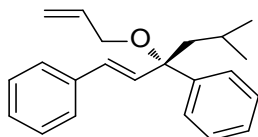
General procedure for the allylation of the α,β -unsaturated tertiary alcohols^[21]:

To a solution of **5** (0.35 mmol) in dry THF (5.0 mL) was added NaH (21.0 mg, 0.53 mmol, 1.5 eq, 60% oil dispersion) under nitrogen, and the resulting mixture was stirred under reflux for 2 h. Then HMPA (0.18 mL, 1.05 mmol, 3.0 eq) was added to the mixture followed by allyl bromide (0.046 mL, 0.53 mmol, 1.5 eq). After the addition, the mixture was stirred under reflux for another 2 h. The reaction mixture was allowed to cool to room temperature, quenched with 2 M aqueous HCl, and extracted with Et₂O. The combined organic phases were washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel (pentane/Et₂O = 100 : 1) to afford diene **6**.

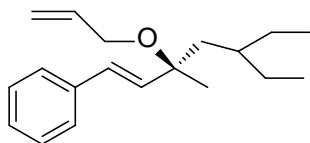


(R)-(E)-3-Allyloxy-3,5-dimethyl-1-phenyl-1-hexene (6a). Light yellow oil (80 mg, 93%). $[\alpha]_D^{20} = -15.4$ (*c* 0.50, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, *J* = 7.2

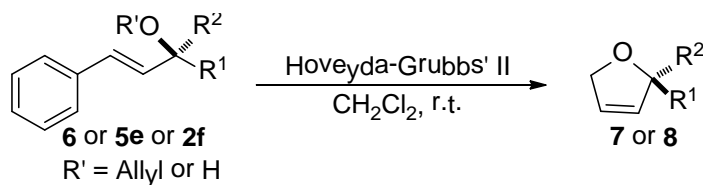
Hz, 2 H), 7.35-7.31 (m, 2 H), 7.26-7.22 (m, 1 H), 6.50 (d, $J = 16.4$ Hz, 1 H), 6.20 (d, $J = 16.4$ Hz, 1 H), 5.99-5.89 (m, 1 H), 5.33-5.28 (m, 1 H), 5.14-5.10 (m, 1 H), 3.91 (d, $J = 5.2$ Hz, 2 H), 1.87-1.80 (m, 1 H), 1.63-1.60 (m, 2 H), 1.41 (s, 3 H), 0.98-0.96 (2 x d, $J = 2.2$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.1, 136.1, 135.5, 129.0, 128.6, 127.4, 126.4, 115.4, 78.0, 63.5, 49.7, 24.7, 24.6, 24.1, 22.9; HRMS (ESI) calcd. for $\text{C}_{14}\text{H}_{19} [\text{M} - \text{OAllyl}]^+$ 187.1481, found 187.1480.



(S)-(E)-3-allyloxy-5-methyl-1,3-diphenyl-1-hexene (6b). Light yellow oil (104 mg, 97%). $[\alpha]_{\text{D}}^{20} = -5.5$ (c 0.66, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.54 (d, $J = 7.2$ Hz, 2 H), 7.46 (d, $J = 7.6$ Hz, 2 H), 7.41-7.35 (m, 4 H), 7.32-7.26 (m, 2 H), 6.75 (d, $J = 16.4$ Hz, 1 H), 6.42 (d, $J = 16.4$ Hz, 1 H), 6.09-5.97 (m, 1 H), 5.44 (dd, $J = 17.2, 1.2$ Hz, 1 H), 5.21 (d, $J = 10.8$ Hz, 1 H), 3.94-3.86 (m, 2 H), 2.13-2.02 (m, 2 H), 1.80-1.72 (m, 1 H), 0.91 (dd, $J = 50.0, 6.4$ Hz, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 143.9, 137.1, 135.6, 134.2, 129.5, 128.6, 128.1, 127.6, 126.9, 126.5, 115.3, 81.8, 63.9, 46.5, 24.5, 24.4, 23.8; HRMS (APCI) calcd. for $\text{C}_{19}\text{H}_{21} [\text{M} - \text{OAllyl}]^+$ 249.1638, found 249.1639.



(R)-(E)-3-Allyloxy-5-ethyl-3-methyl-1-phenyl-1-heptene (6c). Light yellow oil (80 mg, 84%). $[\alpha]_{\text{D}}^{20} = -24.1$ (c 0.49, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.41 (d, $J = 7.2$ Hz, 2 H), 7.36-7.33 (m, 2 H), 7.27-7.24 (m, 1 H), 6.50 (d, $J = 16.4$ Hz, 1 H), 6.21 (d, $J = 16.4$ Hz, 1 H), 5.99-5.92 (m, 1 H), 5.35-5.30 (m, 1 H), 5.14 (dd, $J = 10.4, 1.6$ Hz, 1 H), 3.93 (d, $J = 5.2$ Hz, 2 H), 1.64-1.62 (m, 2 H), 1.42 (s, 3 H), 1.42-1.36 (m, 4 H), 1.29 (s, 1 H), 0.89-0.83 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.1, 136.2, 135.4, 129.2, 128.6, 127.4, 126.4, 115.2, 78.3, 63.6, 45.0, 36.0, 26.9, 26.8, 22.5, 10.82, 10.76; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{23} [\text{M} - \text{OAllyl}]^+$ 215.1794, found 215.1795.

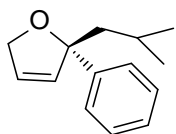


General procedure for the ring-closing metathesis of the dienes^[22]: To a solution of diene (0.29 mmol) in dichloromethane (5 mL) was added Hoveyda-Grubbs' II catalyst (9.4 mg, 0.015 mmol, 0.05 eq) and the resulting mixture was stirred under

nitrogen at room temperature for 2 h. Then the mixture was concentrated in vacuo, and the crude product was purified by column chromatography (pentane/Et₂O = 200 : 1) to afford five-membered ring **7** or **8**.



(R)-2-Isobutyl-2-methyl-2,5-dihydro-furan (7a). Colorless oil (35 mg, 85%). $[\alpha]_D^{20} = -7.5$ (*c* 1.13, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.71 (d, *J* = 6.0 Hz, 1 H), 5.64-5.63 (m, 1 H), 4.58-4.51 (m, 2 H), 1.63-1.55 (m, 1 H), 1.50-1.37 (m, 2 H), 1.19 (s, 3 H), 0.84-0.81 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 134.4, 124.9, 90.4, 74.1, 49.4, 34.1, 24.6, 24.4, 24.3; HRMS (ESI) calcd. for C₉H₁₇O [M + H]⁺ 141.1274, found 141.1276.



(S)-2-Isobutyl-2-phenyl-2,5-dihydro-furan (7b). Colorless oil (53 mg, 90%). $[\alpha]_D^{20} = -94.0$ (*c* 1.08, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.40 (d, *J* = 7.6 Hz, 2 H), 7.35-7.32 (m, 2 H), 7.26-7.21 (m, 1 H), 6.04-6.02 (m, 1 H), 5.86 (d, *J* = 6.0 Hz, 1 H), 4.82-4.78 (m, 1 H), 4.73-4.69 (m, 1 H), 1.89 (dd, *J* = 14.4, 5.6 Hz, 1 H), 1.80 (dd, *J* = 14.4, 6.0 Hz, 1 H), 1.73-1.67 (m, 1 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.88 (d, *J* = 6.8 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 146.5, 133.4, 128.2, 126.4, 125.2, 124.7, 93.8, 74.7, 50.1, 24.6, 24.32, 24.29; HRMS (APCI) calcd. for C₁₄H₁₉O [M + H]⁺ 203.1430, found 203.1427.

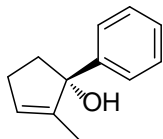


(R)-2-(2-Ethyl-butyl)-2-methyl-2,5-dihydro-furan (7c). Colorless oil (40 mg, 82%). $[\alpha]_D^{20} = -5.7$ (*c* 0.53, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.78 (d, *J* = 6.4 Hz, 1 H), 5.69 (d, *J* = 6.4 Hz, 1 H), 4.64-4.57 (m, 2 H), 1.57-1.52 (m, 1 H), 1.45 (dd, *J* = 14.4, 4.8 Hz, 1 H), 1.39-1.25 (m, 5 H), 1.26 (s, 3 H), 0.85-0.79 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 134.4, 125.0, 90.5, 74.3, 44.0, 36.7, 27.1, 26.8, 26.7, 10.82, 10.80; HRMS (ESI) calcd. for C₁₁H₂₁O [M + H]⁺ 169.1587, found 169.1583.



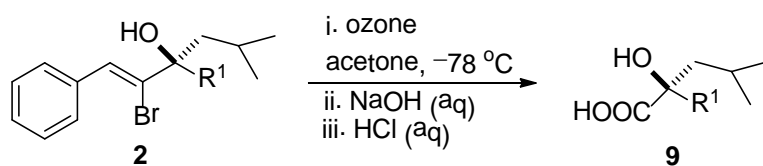
(R)-1-Methyl-2-cyclopenten-1-ol (8a)^[15]. Colorless oil (11 mg, 40%)*. $[\alpha]_D^{20} = +16.8$ (*c* 0.25, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.83-5.81 (m, 1 H), 5.70-5.69 (m, 1 H), 2.51-2.45 (m, 1 H), 2.35-2.29 (m, 1 H), 1.98-1.89 (m, 2 H), 1.68 (br s, 1 H), 1.38 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 137.9, 132.7, 83.4, 39.7, 31.1, 27.4; HRMS (ESI) calcd. for C₆H₉ [M – OH]⁺ 81.0699, found 81.0695.

* This reaction gave full conversion to the desired product, but the yield was diminished due to its volatility.



(S)-2-Methyl-1-phenyl-2-cyclopenten-1-ol (8b). Colorless oil (44 mg, 87%). $[\alpha]_D^{20} = +33.2$ (*c* 0.85, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.32-7.24 (m, 4 H), 7.18-7.15 (m, 1 H), 5.63 (d, *J* = 1.6 Hz, 1 H), 2.44-2.37 (m, 1 H), 2.33-2.25 (m, 2 H), 2.20-2.12 (m, 1 H), 1.86 (s, 1 H), 1.48-1.47 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 146.0, 144.0, 128.7, 128.1, 126.5, 124.8, 87.9, 43.4, 29.4, 11.9; HRMS (ESI) calcd. for $\text{C}_{12}\text{H}_{13} [\text{M} - \text{OH}]^+$ 157.1012, found 157.1008.

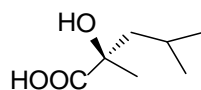
α -hydroxy acids 9: 9a-b and S9c were prepared from **2a-b** and **2g** following the literature procedure,^[24] and **S9c** afforded **9b** following the procedure of literature^[23c]. The absolute configurations of **9a-b** were based on specific rotations reported in literatures.^[23a, 23b]



To a stirred solution of **2** (0.28 mmol) in acetone (7 mL) at $-78\text{ }^\circ\text{C}$ a stream of ozone was bubbled until a blue color persisted in the solution. Subsequently, nitrogen was bubbled through the solution until the blue color had disappeared. Dimethyl sulfide (0.5 mL) and water (1 mL) were added and the mixture was allowed to stir at room temperature for 1 h. The solvent was evaporated and the residue was extracted with ether.

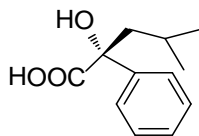
For the products of **2a-b**, the combined organic phases were extracted with 5% NaOH_{aq} , and the combined alkaline phases were acidified with 10% HCl . The resulted solution was extracted with ether. The combined organic phases were dried over MgSO_4 and evaporated to afford **9a-b** as colorless crystals.

For the products of **2g**, the combined organic phases were dried over MgSO_4 and concentrated in vacuo. The crude product was purified by column chromatography (pentane/ Et_2O = 50 : 1) to afford **S9c** as a colorless oil.

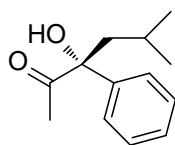


(R)-2-Hydroxy-2,4-dimethyl-pentanoic acid (9a). yield 75%. $[\alpha]_D^{20} = -10.4$ (*c* 0.56, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 1.83 – 1.75 (m, 2 H), 1.69 – 1.66 (m, 1 H),

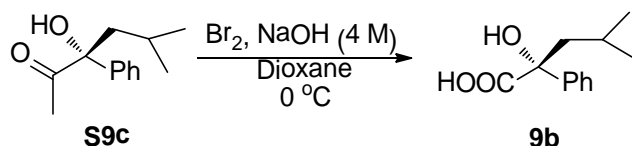
1.47 (s, 3 H), 0.96 (d, $J = 5.2$ Hz), 0.89 (d, $J = 5.6$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 180.0, 72.0, 45.6, 24.9, 21.8, 21.7, 20.5.



(R)-2-Hydroxy-4-methyl-2-phenyl-pentanoic acid (9b). yield 86%. $[\alpha]_{\text{D}}^{20} = -10.0$ (c 1.16, CHCl_3), $[\alpha]_{\text{D}}^{20} = -72.4$ (c 1.16, EtOH); ^1H NMR (400 MHz, CDCl_3) δ 7.29 - 7.27 (m, 2 H), 7.01 - 6.92 (m, 3 H), 1.81 - 1.68 (m, 2 H), 1.50 (s, 1 H), 0.61 (d, $J = 8.0$ Hz, 3 H), 0.56 (d, $J = 4.0$ Hz). The absolute configuration was based on specific rotation reported in the literature: **9b** $[\alpha]_{\text{D}}^{22} = -16.7$ (c 0.83, EtOH).



(R)-3-Hydroxy-5-methyl-3-phenyl-2-hexanone (S9c). Colorless oil (46 mg, 79%). $[\alpha]_{\text{D}}^{20} = -16.9$ (c 0.43, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.42-7.39 (m, 2 H), 7.30-7.26 (m, 2 H), 7.23-7.19 (m, 1 H), 4.46 (s, 1 H), 2.13-2.06 (m, 2 H), 2.04 (s, 3 H), 1.79-1.72 (m, 1 H), 0.90-0.85 (m, 6 H); ^{13}C NMR (100 MHz, CDCl_3) δ 209.9, 141.7, 128.5, 127.8, 126.1, 82.8, 44.9, 24.6, 24.2, 23.8, 23.7; HRMS (ESI) calcd. for $\text{C}_{13}\text{H}_{17}\text{O}$ $[\text{M} - \text{OH}]^+$ 189.1274, found 189.1268.



To a solution of **S9c** (40 mg, 0.19 mmol) in dioxane (3 mL) was added NaOH (10 mL, 4 M). The resulting suspension was stirred vigorously at 0 °C while bromine (0.030 mL, 0.57 mmol) was added slowly. The resulting mixture was stirred for another 5 min after the addition was finished. Then the mixture was washed with ether. The aqueous layer was acidified with 1 M HCl and extracted with ether. The combined organic phases were dried over MgSO_4 , filtered and concentrated in vacuo. The residue was further purified by chromatography on silica gel (EtOAc : pentane = 6 : 1/ 1% AcOH) to afford **9b** (8 mg, 20 %) which showed to be identical to the ozonolysis product of **2b**. $[\alpha]_{\text{D}}^{20} = -7.8$ (c 0.25, CHCl_3).

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